

REMARKS

Claims 1-49 are pending in this application. Claims 20-49 are withdrawn from consideration, as a result of the restriction requirement imposed in the Office Action mailed November 1, 2005.

Independent claims 1, 10, and 19, as well as withdrawn independent claims 20, 31, and 39, have been amended to clarify that “TFPI” refers to the polypeptide tissue factor pathway inhibitor. Support is found in the specification, for example, at page 1, paragraph [03]. Claim 19 has also been amended to correct a typographical error in the word “arginine”.

The amendments add no new matter.

**Objection to Claims 1-19**

Claims 1-19 are objected to as reciting “TFPI”. As suggested in the Office Action, Applicants have amended each independent claim to recite the full name of the protein, tissue factor pathway inhibitor.

Withdrawal of the objection is respectfully requested.

**The Rejections of Claims 1-17 under 35 U.S.C. § 102**

Claims 1-17 are rejected as being anticipated by

- Dorin *et al.*, U.S. Patent No. 6,319,896 (“Dorin”);
- Diaz-Collier *et al.*, EPO publication EP 0 559 632 A1 (“Diaz-Collier”);
- Chen *et al.*, U.S. Patent No. 6,525,102 (“Chen”); and
- Creasey, PCT Publication WO 03/032904 (“Creasey”).

Applicants respectfully traverse these rejections.

Independent claims 1 and 10 (and their dependent claims 2-9 and 11-17, respectively) recite purified preparations and pharmaceutical compositions comprising a plurality of TFPI or TFPI analog molecules. Less than about 12% of the TFPI or TFPI analog molecules are modified species. Modified species have one or more of the following modifications: oxidation, carbamylation, deamidation, cysteine adducts, aggregation, and misfolding.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). None of the references Dorin, Diaz-Collier, Chen, or Creasey meets this legal standard of either express or inherent anticipation.

First, the references do not expressly describe all the elements of claims 1 or 10. As the Office Action acknowledges, the TFPI compositions of Dorin, Diaz-Collier, Chen, and Creasey all fail with respect to indicating the amounts of oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded species present. Office Action at page 4, lines 16-17; page 5, lines 13-15; and page 6, lines 11-14.

Second, it is black letter law that inherent anticipation requires that the inherent element necessarily is present in the single reference:

a prior art reference may anticipate without disclosing a feature of the claimed invention if that characteristic is necessarily present, or inherent, in the single anticipating reference.

*Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003) (emphasis added). None of the references Dorin, Diaz-Collier, Chen, or Creasey meets this legal standard of an inherently anticipating reference. That is, these references do not necessarily disclose purified preparations or pharmaceutical compositions comprising TFPI or TFPI analog molecules “wherein less than about 12% of the TFPI or TFPI analog molecules are modified species

[oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded]” as recited in independent claims 1 and 10. The specification in fact provides objective experimental evidence that the methods disclosed in the cited references do not yield TFPI compositions having the claimed purity.

Dorin

Applicants have analyzed TFPI compositions prepared as described in the art and found that

The purification method of the invention produces preparations of TFPI or TFPI analog molecules that contain fewer modified TFPI or TFPI analog species than previous purification methods described in Gustafson *et al.*, *Protein Expression and Purification* 5, 233-41, 1994; WO 96/40784; U.S. Pat. No. 6,319,896 [Dorin]; and U.S. Pat. No. 6,323,326 ("Process B").

Specification, paragraph [63] at page 17 (emphasis added). Specifically, Applicants have compared “the purity of recombinant ala-TFPI produced using Process B [described in Dorin] and using the method of the invention.” Specification, paragraph [65] at page 17. The process disclosed in Dorin (“Process B”) resulted in a purity of 75%, as determined by reversed phase high performance liquid chromatography (CN HPLC). Specification, Table 1 at page 18. The CN HPLC method “is used to detect modified TFPI or TFPI analog species, i.e., TFPI or TFPI analog molecules with modifications such as oxidized methionine residues, and amino acid modifications such as residual N-terminal methionine, carbamylation, deamidation, and acetylation” and also “species having substitutions of norleucine for methionine.”<sup>1</sup> Specification, paragraph [44] at page 12.

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<sup>1</sup> Some species detected by CN HPLC, namely (1) species having an N-terminal methionine, (2) acetylated species, and (3) species having substitutions of norleucine for methionine, are not “modified species,” as recited in claims 1 and 10. However, as indicated in Table 1 at page 18 of the specification, the total amount of (1), (2) and (3) in the process disclosed in Dorin (“Process B”) is less than about 2.6%, such that the amount of “modified species” comprising oxidized, carbamylated, and deamidated species totaled about 22% (or 100% minus the measured purity: 75% + about 2.6%).

Thus, the CN HPLC analysis alone shows that the process disclosed in Dorin does not provide TFPI compositions comprising TFPI or TFPI analog molecules “wherein less than about 12% of the TFPI or TFPI analog molecules are modified species,” as recited in independent claims 1 and 10. The process disclosed by Applicants (“Process C”), however, resulted in a purity of 90%<sup>2</sup>, as determined by CN HPLC. Specification, Table 1 at page 18. Additional analyses showed less than 1% carbamylated species (>99% purity by cation exchange chromatography), no detectable cysteine adduct, less than 2% aggregated species (>98% purity by size exclusion chromatography), and less than 2% misfolded species (>98% purity by SDS-polyacrylamide gel electrophoresis).

In view of the above results, the process disclosed in Dorin does not result in TFPI preparations or pharmaceutical compositions as recited in claims 1 and 10. Dorin therefore does not inherently anticipate these claims.

Diaz-Collier

The TFPI preparation process described in Diaz-Collier is similar to that described in Dorin (discussed above) and would therefore be expected to provide TFPI compositions having similar amounts of modified (oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded) species. In particular, Diaz-Collier describes a TFPI preparation and purification process in which TFPI is expressed in *E. coli*. The inclusion bodies containing TFPI are isolated and subjected to either sulfitolysis or reduction with  $\beta$ -mercaptoethanol. The product is purified using ion exchange chromatography, and refolded by disulfide interchange reaction. The refolded, active TFPI is then purified by cation exchange chromatography. Diaz-Collier,

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<sup>2</sup> As indicated in Table 1 at page 18 of the specification, the total amount of (1) species having an N-terminal methionine, (2) acetylated species, and (3) species having substitutions of norleucine for methionine (which, as explained in footnote 1, are not “modified species” of claims 1 and 10), as detected by CN HPLC, was less than about 2.3%. The amount of “modified species” comprising oxidized, carbamylated, and deamidated species therefore totaled about 8% (or 100% minus the measured purity: 90% + about 2.3%).

page 2, lines 32-48. Essentially the same method is referenced in Dorin at column 14, lines 16-26<sup>3</sup>.

Consistent with these similar TFPI synthesis methods, the TFPI preparations disclosed in Diaz-Collier and Dorin do not satisfy the purity criteria recited in claims 1 or 10. This is despite the Office Action's contentions that

The '632 publication [Diaz-Collier] teaches that a TFPI preparation refolded and purified by the method disclosed therein was greater than 95% homogeneous suggesting that there was minimal misfolding, aggregation, carbamylation, oxidation, deamidation, or cysteine adducts. There is also no evidence or indication that the preparation of the '632 publication contains TFPI polypeptides that have cysteine adducts or are misfolded, aggregated, carbamylated, oxidized, or deamidated.

Office Action, page 6, lines 8-14. The >95% level of homogeneity cited above in Diaz-Collier clearly refers to "the material produced from Example 1," as analyzed using a single method, namely Electrospray Mass Spectral Analysis (EMS). Diaz-Collier, page 11, line 55 to page 12, line 3. This single method however cannot detect all modified species. As is well known in the art, EMS involves ionizing a sample and determining its mass to charge ratio. "Interpreting Electrospray Mass Spectra" at <http://www.ionsource.com/tutorial/spectut/>, page 2. Some types of modified species, however, will exhibit the same or almost the same observed mass to charge ratio as unmodified species. This results in a level of "homogeneity," as determined by EMS, that does not reflect the actual percentage of modified (oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded) species according to claims 1 and 10.

For example, a TFPI dimer (an aggregated, modified species) upon ionization will have twice the charge but also twice the mass as a TFPI monomer (an unmodified species). The particular modification of dimerization (or aggregation) therefore does not affect the mass to

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<sup>3</sup> Dorin has found that a polyionic polymer (*e.g.*, heparin or dextran sulfate) can facilitate the solubilization, formulation, purification, and refolding or recombinantly produced TFPI. Dorin, Abstract and column 13, lines 50-60.

charge ratio. Native TFPI and aggregated (or a particular type of modified) TFPI are therefore “homogeneous” using EMS. For this reason, it is well documented that “Dimer formation can be a major problem in [Electrospray Mass Spectral] analyses.” “Interpreting Electrospray Mass Spectra”, page 7. The same difficulty applies to the detection of trimers or higher molecular weight aggregates.

Indeed, using the separate analysis of polyacrylamide gel electrophoresis, Diaz-Collier found that “the TFPI from in Example 1 [having >95% homogeneity based on EMS] had a higher content of dimer species [than TFPI from Example 2, containing up to 30% heterogeneous species based on EMS].” Diaz-Collier, page 11, lines 35-39 (emphasis added). This finding clearly undermines the Office Action’s assertion above of “no evidence or indication that the preparation of the ‘632 publication [Diaz-Collier] contains TFPI polypeptides that . . . are . . . aggregated.” Diaz-Collier in fact provides explicit evidence of aggregates in the TFPI produced in Example 1, alleged to anticipate the pending claims.

*Chen and Creasey*

Chen refers to known, recombinant TFPI synthesis methods. Chen, column 17, lines 5-26. In fact, the same buffer exchange via dialysis at 4°C, used for the particular TFPI formulations in Chen’s examples, is also described in Dorin. Compare Chen, column 36, lines 44-46 and Dorin, column 17, lines 15 and 16. Creasey likewise refers to known recombinant TPFPI production and purification methods, including the same methods described in Dorin, as discussed above. Creasey, paragraph [45] at page 14. In view of Applicants’ results obtained using the process disclosed in Dorin, there is no basis for concluding that either Chen or Creasey describes a purified TFPI preparation or pharmaceutical composition within the scope of claim 1 or 10.

The Office Action, nevertheless, asserts inherent anticipation because

The '102 patent [Chen] teaches that adding arginine, lysine, aspartic acid, or glutamic acid to a TFPI polypeptide composition protects TFPI from aggregation (Col. 6, lines 8-55) . . . The '102 patent also teaches that the amino acids have inhibitory effects on deamidation (Col. 7, lines 20-47) . . . The '102 patent teaches that methionine or EDTA can be added to the TFPI composition to protect the polypeptide against oxidation (Col. 10, lines 21-43).

Office Action, page 4, lines 8-16. The cited passages in Chen, however, all clearly relate to stabilizing TFPI against aggregation, deamidation, and oxidation over time (*i.e.*, during storage). “The increased storage stability of the composition is achieved through the influence of the amino acid on stability of the therapeutically active polypeptide, more particularly its influence on polypeptide aggregation during storage in liquid formulations.” Chen, column 6, lines 17-21 (emphasis added). “Increased storage stability of the stabilized liquid polypeptide-containing compositions of the invention may also be associated with the inhibitory effects of the amino acid base on deamidation of glutamine and/or asparagine residues within the therapeutically active polypeptide during storage.” Chen, column 7, lines 20-25 (emphasis added). “In this manner, the amino acid methionine may be added to inhibit oxidation . . . By ‘inhibit’ is intended minimal accumulation of methionine oxidized species over time.” Chen, column 10, lines 26-32 (emphasis added).

The ability to stabilize against the formation of modified species over time (*i.e.*, during storage) has no bearing on the ability to provide a purified composition, having an initially low amount of modified species. Stabilization involves reducing the rate of an undesired reaction (*e.g.*, oxidation), regardless of the initial amount of undesired species present (*e.g.*, oxidized species). Chen’s focus is in improving TFPI stability, as measured by its half-life with respect to various degradation mechanisms such as oxidation and aggregation. Chen, Figures 9-11 and Example 8.

Regarding the initial purity of the TFPI compositions prepared (*e.g.*, recombinantly), Chen and Creasey simply refer to the same TFPI synthesis procedures described above in Dorin and Diaz-Collier. As Applicants have demonstrated, these procedures resulted in amounts of modified (oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded) TFPI species outside the scope of claims 1 and 10.

Case Law

The Office Action cites *Ex parte Phillips*, 28 U.S.P.Q. 1302, 1303 (BPAI 1993); *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 1977); and *Ex parte Gray*, 10 U.S.P.Q.2d 1922, 1923 (BPAI 1989) for the proposition that

The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences.

Office Action, page 4, line 17 to page 5, line 1; page 5, lines 15-20; and page 6, lines 14-19. The holdings in these cases, however, all rely on the complete lack of objective evidence (or an inventor declaration) rebutting the Examiner's assertion of inherent anticipation: "There is no evidence of record which establishes that the respective antigens do, in fact, differ or the significance of such a difference." *Ex parte Phillips*, 28 U.S.P.Q. at 1303. "[Appellants] have not provided any effective argument nor submitted any evidence that a gas stream does not inherently remove generated ammonia." *In re Best*, 562 F.2d at 1254. "[N]o objective evidence has been provided establishing that no method was known to those skilled in this field whereby the claimed material might have been synthesized." *Ex parte Gray*, 10 U.S.P.Q.2d at 1926.

In contrast to the facts of these cases, Applicants have provided objective evidence rebutting the Office Action's assertions that the pending claims are inherently anticipated. As



explained above, this evidence is found in the side-by-side comparison in the specification, showing in particular that TFPI compositions made by the methods disclosed by Applicants fall within the scope of independent claims 1 and 10, while prior art TFPI compositions do not.

Claims 2-9 and 11-17 depend from claims 1 and 10, respectively, and are therefore patentable for at least the same reasons given above with respect to claims 1 and 10.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 are respectfully requested.

### **The Rejections of Claims 18 and 19 under 35 U.S.C. § 103**

Claims 18 and 19 are rejected as obvious over Chen in view of Diaz-Collier. Applicants respectfully traverse these rejections.

Claims 18 and 19 are directed to pharmaceutical compositions comprising a plurality of ala-TFPI molecules. Less than about 12% of the ala-TFPI molecules are modified species. Modified species have one or more of the following modifications: oxidation, carbamylation, deamidation, cysteine adducts, aggregation, and misfolding. Claim 19 additionally recites that the pharmaceutical formulation comprises 20 mM sodium citrate, 300 mM L-arginine, and 5 mM methionine, at pH 5.5.

A *prima facie* case of obviousness requires that the prior art reference (or references when combined) teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985, 180 U.S.P.Q. 580, 583 (C.C.P.A. 1974) (emphasis added). For the same reasons given above with respect to the rejections under 35 U.S.C. § 102, neither Chen nor Diaz-Collier expressly or inherently describes or suggests a TFPI pharmaceutical composition (let alone an ala-TFPI pharmaceutical composition) “wherein less than about 12% of the ala-TFPI molecules are modified species [oxidized, carbamylated, deamidated, cysteine adduct, aggregated, and/or misfolded]” as recited in claims 18 and 19. Chen and/or Diaz-Collier therefore do not establish a *prima facie* case of obviousness.

In contrast to the disclosures of Chen and Diaz-Collier (as well as Dorin and Creasey), Applicants have discovered a “purification method [that] produces preparations of TFPI or TFPI analog molecules that contain fewer modified TFPI or TFPI analog species than previous purification methods . . . The purification is of TFPI or TFPI analog is largely achieved after the folding step by a sequence of chromatography operations.” Specification, paragraphs [63] and [64]. The sequence of chromatography operations, as set forth in detail throughout Applicants’ specification, is not found in the prior art. The purification method disclosed by Applicants results in TFPI or TFPI analog compositions having the claimed, patentably distinct characteristics.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully requested.

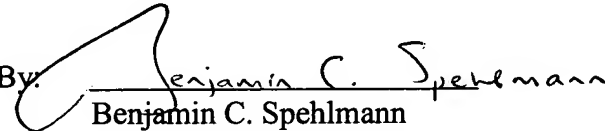
CONCLUSION

In view of the above amendments and remarks, all pending claims of this application are believed to be in condition for allowance. Acknowledgement of the same is respectfully requested. This response is believed to completely address all of the substantive issues raised in the Office Action dated February 23, 2006.

Please continue to direct all correspondence in this application to Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

Date: May 23, 2006

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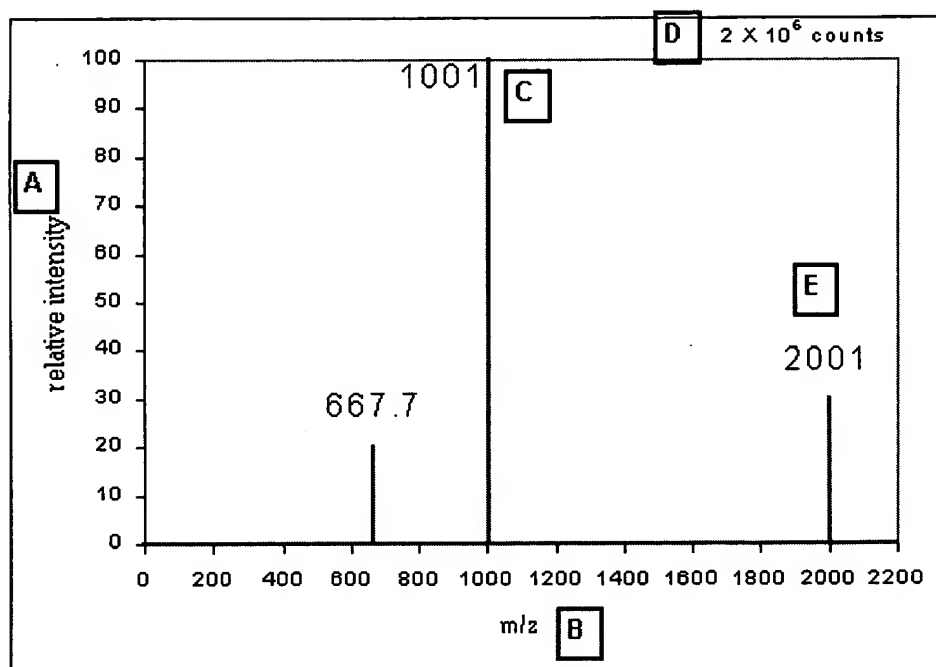
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# Interpreting Electrospray Mass Spectra

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## Key to the "Average" Mass Spectrum



## -The Key

- A** The Y axis is labeled relative intensity. This is the intensity relative to the tallest peak in the spectrum with the tallest peak set to 100%.
- B** The X axis is mass divided by charge, m/z. For example if the mass of a molecule is 2000 u and the

molecule possesses two proton adducts its  $m/z$  value is equal to  $(2000+2)/2$ , the  $m/z$  value read on the spectrum is 1001.

- C This is the tallest peak in the spectrum also known as the "base peak"
- D A spectrum will have a certain number of counts associated with the tallest peak in the spectrum. This number can be used to gauge the relative intensity or concentration of the analyte. One should be forewarned that the count number is relative and can be adjusted with the multiplier gain and strictly speaking cannot be related to concentration without an internal standard. Counts will also be affected by spray needle and overall source maintenance.
- E All of the peaks in a spectrum are just that, peaks and should not be referred to as ions, strictly speaking they are peaks in a spectrum. Why are "mass spec. types" so strict?

**Note:**

1. It is common to overhear people talking about the "molecular ion" while pointing at an electrospray peak. Molecular ions are not generally observed in the electrospray ionization process. A molecular ion is formed by the loss of an electron. In the electrospray process, ionization is accomplished by the loss or gain of a proton (or other adduct), some refer to this ion as the "pseudo molecular ion."
2. The electrospray process usually produces a population of multiply charged molecules and this population is accurately reflected in the intensity of the peaks in the spectrum.
3. In positive ion mode the number of charged species normally observed in an electrospray spectrum is reflected in the number of basic sites on a molecule that can be protonated at low pH.




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Last updated: Monday, July 18, 2005 01:43:20 PM


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# Interpreting Electrospray Mass Spectra

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## Tips for Looking at Electrospray Spectra And Frequently Asked Questions

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### "Peak Tips"

#### "What I normally look for in a spectrum"

- 1) **Look for the tallest peak in the spectrum** above 200 mass units. (The low end of a spectrum can often be confounded with solvent noise.) Then look for peaks that are roughly double or half the mass. This may tell you whether there are multiply charged species present which can help with mass determination.
- 2) **Counts.** Resist interpreting meager spectra. If you know that on a particular day that  $1.0 \times 10^6$  is a respectable, reliable signal then you will know that a spectrum that tops out at  $1.0 \times 10^4$  counts (or at background) may not be a reliable spectrum to interpret.
- 3) **The quality of the spectrum is important.** You will waste valuable time interpreting a low quality spectrum. If you are not happy with the quality of the spectrum try averaging several or many low level spectra to obtain a better quality "averaged mass spectrum." Compare this to a background spectrum to see if the peaks really stand out.
- 4) **Reproducibility is important.** The peak must be consistent to be considered a relevant peak. You should not lend credence to what I call "one scan wonders."

**5) Determining the charge state of a peak when only one peak is obvious**

A molecule will often have adduct ions associated with it other than hydrogen. Look for sodium or ammonium adducts. These adducts can often give you a hint as to the charge state of a peak. For example if there is only one major species in a spectrum look for the sodium adduct following that peak. If it is a singly charged species the sodium adduct will be found at +22 mass units higher than the M+H peak. If the peak is doubly charged the adduct will appear at +11 mass units.

**Isotopes**

If the mass spectrometer you are working with has sufficient resolution look at the isotopes, a singly charged ion will show isotopic peaks that differ by 1 mass unit, a doubly charged ion will show peaks that differ by 0.5 mass units and so on. This is another way to deduce the charge state of a peak and thus the mass.

## Frequently Asked Questions

**Q** How can I tell if a peak is real?

**A** Wow, this is some question. All peaks are real. In an LC/MS run we look for peaks that reoccur in multiple adjacent scans (spectrums) but not in every scan. If the peak occurs in every scan it may be a background peak. It is possible to get system noise or spikes that only occur in one scan or sporadically these are most likely electronic or some other form of system noise.

**Q** How can I be sure of the identity of a peak.

**A** Well, a mass is just a mass and many compounds have isobaric mass so you can't be sure from just a mass. In the old days we would perform an enzymatic digest on a protein, run an LC/MS peptide map and match up the mass with the theoretical fragments. Today the bar is rightly higher and we go one step further in the identification, we take the peak through a fragmentation and match up the fragment masses with the theoretical CID fragment masses for that peptide. This gives us a positive ID.

Another overlooked component in LC/MS is part of what makes LC/MS so powerful and that is the correlation of mass and LC retention time. If the retention time of a molecule has been previously characterized this information can be linked with the mass information for a positive ID.

If you are characterizing a new molecule try modifying the molecule to see if you can modify the mass. Try an enzyme digest if the unknown is a protein or try chemical modification if it is a small molecule and see if the mass of the unknown changes as predicted by the mass ID.

**Q** How can I differentiate a compound at one mass from another at twice the mass? For example a compound with mass 1000 will display peaks at m/z 1001 and 501, and a compound with mass 2000 may display peaks at m/z 2001, 1001, 666.7 and 501. The mass determination can further be confounded if the peptide at 1000 forms dimers during the

electrospray process.

- A
- 1) The peak envelope does not skip peaks, for example the 2000 mass even if it does not have an obvious peak at 2001 it should have the 666.7 peak between the 1001 and 501 peaks.
  - 2) Also try to determine the charge state of the ions from the adducts or from the isotopes. This will tell you what the mass of the compound is.
  - 3) Dimer formation can be a major problem in some analyses. Try to reduce the concentration of the analyte. Often if the concentration is too high dimers will be observed in the spectrum. Also dimers can be reduced by changing some of the setting on the mass spectrometer.
  - 4) With the peak envelope of larger molecules (10kDa+) look for smooth peak distributions. The peak distribution should have a smooth bell shaped curve appearance, sometimes trailing off to the right. The peak to peak relationship should be predictable, if one observes an alternating pattern of peak intensities this may be a clue to a coeluting dimer.
- Q I believe that I am observing artifctual fragmentation and do not know which peaks are real.
- A Again all peaks are real. Sometimes on can induce fragmentation before the first mass filter (in-source CID, source CID). While this effect can be a valuable characterization strategy for those possessing single quadrupole instruments it is often a distraction when fragmentation is not the goal. My suggestion is to try and slow the ions down so that they will not collide and fragment with the residual atmosphere in the source.



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Last updated: Monday, July 18, 2005 01:43:20 PM